June 9, 2019

Ke-Qin Hu, Koo Jeong Kang, Nikolaos Pyrsopoulos
Editor-in-Chief
World Journal of Hepatology

Re: Manuscript NO.: 48762 “Efficacy of long-term rifaximin treatment for hepatic encephalopathy in the Japanese.”

Dear Editors:

Thank you for the opportunity to revise our manuscript. We found the reviewer’s comments helpful. We have taken all of the reviewers’ comments into account and are now submitting a revised version of the manuscript.
Below, please find a detailed response to the reviewers’ comments. Changes in the manuscript are marked within the revised manuscript by highlighting. We hope that this revised manuscript now meets the criteria for publication in *World Journal of Hepatology.*

Respectfully yours,

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RESPONSE TO REVIEWER 1

We thank the reviewer for these critical comments that have helped us to improve our paper considerably. As indicated in the following responses, we have taken these comments and suggestions into account in the revised version of our paper.

Comment: *This retrospective study was done by appropriate statistical methods, is well presented, with one exception, and has clinical importance. Its deficit is the small number of patients studied. The study has three key findings: (a) that rifaximin causes sustained reduction of the blood ammonia level in patients with hepatic encephalopathy, (b) that long-term rifaximin treatment did not worsen liver function and had minimal side effects, and (c) that the decrease in blood ammonia level was less in patients with larger diameter of the portosystemic shunt. The small number of patients combined with the fact that mortality did not differ between the group that received rifaximin and the group that did not does not allow, in this reviewer's opinion, any conclusion about the effect of rifaximin on death from hepatic encephalopathy. That one patient in the control group died from sepsis is inadequate as an argument for such an effect of rifaximin. I strongly suggest that the last sentence in the Results section of the Abstract "This suggests that...may be suppressed by rifaximion use>" and a similar statement in the Discussion are removed.*

Response: Thank you for your important comment. We agree with this comment and have removed “This suggests the possibility that death from hepatic encephalopathy may be suppressed by rifaximin use” in the Results section of the Abstract. We have removed “helps decrease the death rate associated with it” in the Conclusion section. Also, we removed the sentence “while rifaximin prevented death caused by HE in patients” in the Discussion. Instead, we mentioned that “We can therefore infer that rifaximin cannot treat liver cirrhosis itself, and that is the limitation of this treatment.” (Page 17, Line 391-392)

RESPONSE TO REVIEWER 2

We thank the reviewer for these critical comments that have helped us to improve our paper considerably. As indicated in the following responses, we have taken these comments and suggestions into account in the revised version of our paper.

Comment 1: I applaud the efforts made by authors, but I have major concerns. As correctly stated by authors, not having studied the West haven grade zero HE as per .....Journal og Gastroenterology. Volume 42, Issue 1, January 2007, Pages 79-82....is a great limitatioin that lessens of importance their study. Authors are warmely advised to comment at large on this issue, not putting it as limitation and that is all.

Response1: Thank you for your important comment. As you pointed out, the West Haven test was insufficient to identify subclinical encephalopathy and we should use the Trail Making Test to evaluate minimal encephalopathy. We are sorry, but we could not evaluate the Trail Making Test in this retrospective study.

In consideration of your comments, we added the description that "West Haven criteria is used to assess HE[19]. However the West Haven test is not sufficient to identify subclinical encephalopathy and the Trail Making Test was more useful to detect minimal encephalopathy[20]. In this retrospective study, we could not evaluate the Trail Making Test." to emphasize the importance of evaluating minimal encephalopathy. (Page 15, Line 353-357)

Reference 19: Conn HO, Liberathal MM. The hepatic coma syndromes and lactulose. Williams and Wilkins; 1979:1-121 [DOI: https://doi.org/10.1016/0016-5085(79)90191-4]

Reference 20: Citro V, Milan G, Tripodi FS, Gennari A, Sorrentino P, Gallotta G, Postiglione A, Tarantino G.Mental status impairment in patients with West Haven grade zero hepatic encephalopathy: the role of HCV infection. J Gastroenterol 2007; 42:79-82 [PMID: 17322997 DOI: 10.1007/s00535-006-1978-8]

Comment 2: The importance of ammonia levels should be debated by authors in the Discussion section at the light of the following studies, putting in evidence the difference in findings between their results and the previous ones. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol. 2009 Nov 24;9:89. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol. 2009 Mar 17;9:21. Finally, thinking of the survival of cirrhotics in terms of presence of shunts is a little

bit reductive, playing a lot of factors, i.e., infections, malnutrition, CV disease, cancer and so on.

Response 2: Thank you for your helpful comment and we agree with your comment. In consideration of your comments and What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol. 2009 Nov 24;9:89, we have now added the following to the revised manuscript "Previous report indicated that spleno-renal shunts are burdened by an increased incidence of HCC[24]. We also need to be aware of the existence of HCC." (Page 17, Line 392-394)

Reference 24: Tarantino G, Citro V, Conca P, Riccio A, Tarantino M, Capone D, Cirillo M, Lobello R, Iaccarino V. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterology 2009; 9:89 [PMID: 19930687 DOI: 10.1186/1471-230X-9-89]

In consideration of your comments and Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol. 2009 Mar 17;9:21, we added the following to the revised manuscript "One previous study reported that the grade of portosystemic collateral veins was concordant with ammonia levels[21]. This finding was consistent with our results" (Page 16, Line 361-363) and "This result suggests that although rifaximin improved overt HE, minimal HE may remain in cases with large shunts and that the grade of portosystemic shunts affected the serum level of ammonia as stated in the previous report[21]. (Page 16, Line 371-374)

Reference 21: Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, Tripodi FS, Cirillo M, Lobello R. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterology 2009; 9:21 [PMID: 19292923 DOI: 10.1186/1471-230X-9-21]

Finally, as you suggested, we have now mentioned the following in the revised manuscript: "This was a retrospective study of a few cases in a single institution, and it is necessary to evaluate a larger number of cases in a multiple-center study to assess survival. It is also necessary to consider HCC, infections, malnutrition, and cardiovascular disease, etc. as causes of death in patients with liver cirrhosis." (Page 17, Line 398-402)